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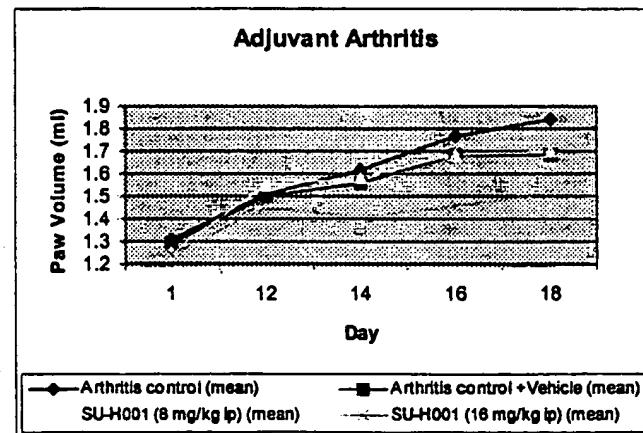
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)™

(51) International Patent Classification ⁶ :	A3	(11) International Publication Number: WO 99/48868
C07D 209/34, 403/06, 409/06, A61K 31/40, 31/415		(43) International Publication Date: 30 September 1999 (30.09.99)
(21) International Application Number: PCT/US99/06468		Washington Square West, New York, NY 10011 (US). SHAWVER, Laura, K. [US/US]; 216 Cotter Street, San Francisco, CA 94112 (US). SUN, Li [CN/US]; 64 Rock-harbor Lane, Foster City, CA 94404 (US). TANG, Peng, C. [US/US]; 827 Camino Ricardo, Moraga, CA 94556 (US). ULLRICH, Axel [DE/DE]; Turkenstrasse 104, D-80799 München (DE).
(22) International Filing Date: 26 March 1999 (26.03.99)		(74) Agents: WARBURG, Richard, J. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).
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60/080,422 2 April 1998 (02.04.98) US		
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(54) Title: HETEROCYCLIC CLASSES OF COMPOUNDS FOR THE MODULATING TYROSINE PROTEIN KINASE

(57) Abstract

The invention relates to certain indolinone-based and pyrazolylamide-based compounds, their method of synthesis, and combinatorial libraries consisting of the compounds. The invention also relates to methods of modulating the function of protein kinases using these compounds and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways.



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06468

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	C07D209/34	C07D403/06	C07D409/06	A61K31/40	A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 50356 A (SUGEN INC) 12 November 1998 (1998-11-12) * overlap of chemical formula, see claim 1, definition of Q = 3,5 * the whole document ---	1-7,62
X	WO 98 07695 A (HIRTH KLAUS PETER ;SHAWVER LAURA KAY (US); SUGEN INC (US); TANG PE) 26 February 1998 (1998-02-26) * overlap of chemical formula, see e.g. claim 6, definition of R8 and R9, claim 10, defintion of R5 and R6 etc. * the whole document ---	39-61
X	WO 98 07695 A (HIRTH KLAUS PETER ;SHAWVER LAURA KAY (US); SUGEN INC (US); TANG PE) 26 February 1998 (1998-02-26) * overlap of chemical formula, see e.g. claim 6, definition of R8 and R9, claim 10, defintion of R5 and R6 etc. * the whole document ---	1-7,62
Y	WO 94 14808 A (ERBA CARLO SPA) 7 July 1994 (1994-07-07) cited in the application the whole document ---	39-61
Y	WO 94 14808 A (ERBA CARLO SPA) 7 July 1994 (1994-07-07) cited in the application the whole document ---	1-7,62
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

16 November 1999

Date of mailing of the international search report

10.12.99

Name and mailing address of the ISA

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Stellmach, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SPADA A P ET AL: "SMALL MOLECULE INHIBITORS OF TYROSINE KINASE ACTIVITY" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 5, no. 8, 1 January 1995 (1995-01-01), pages 805-817, XP000567587 ISSN: 1354-3776 * see page 812, Fig.2, page 813, Tab.1 * the whole document ---	1-7,62
Y	WO 96 00226 A (PHARMACIA SPA ;BUZZETTI FRANCO (IT); BRASCA GABRIELLA MARIA (IT)); 4 January 1996 (1996-01-04) the whole document ---	8-19
X	WO 96 16964 A (PHARMACIA SPA ;BUZZETTI FRANCO (IT); BRASCA GABRIELLA MARIA (IT)); 6 June 1996 (1996-06-06) the whole document ---	39-50
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Y	TRAXLER,P.M.: "Protein tyrosine kinase inhibitors in cancer treatment" EXP.OPIN.THER.PATENTS, vol. 7, no. 6, 1997, pages 571-588, XP002122590 LONDON * see p.584, par. 8.2 * the whole document ---	1-19, 39-62
X	WO 92 20642 A (RHONE POULENC RORER INT) 26 November 1992 (1992-11-26) * overlapping chemical formula * the whole document ---	8-19,62
Y	WO 95 24190 A (YISSUM RES DEV CO ;SUGEN INC (US)) 14 September 1995 (1995-09-14) " see fig 3e, p.3/12, ex. M17, M18 * the whole document ---	8-19,62
		-/-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>LEVITZKI A ET AL: "TYROSINE KINASE INHIBITION: AN APPROACH TO DRUG DEVELOPMENT" SCIENCE, US, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 267, March 1995 (1995-03), page 1782-1788 XP002048355 ISSN: 0036-8075 * see p.1784/1785, ex.AG1112 * the whole document</p> <p>---</p>	8-19,62
Y	<p>GAZIT,A. ET AL.: "Tyrphostins. 2. Heterocyclic and alpha-Substituted Benzylidenmalonitirile Tyrphostins as Potent Inhibitors of EGFR Receptor and ErbB2/neu Tyrosine Kinases" J.MED.CHEM., vol. 34, no. 6, June 1991 (1991-06), pages 1896-1907, XP000472938 WASHINGTON * see p.1897, table 1, ex. 11 * the whole document</p> <p>---</p>	8-19,62
Y,P	<p>SUN,LO. ET AL.: "Synthesis and Biological Evaluation of 3-Substituted Indolin-2-ones : A novel Class of Tyrosine Kinase Inhibitors That Exhibit Selectivity toward Particualr Receptor Tyrosine Kinases" J.MED.CHEM., vol. 41, no. 14, 2 July 1998 (1998-07-02), pages 2588-2603, XP002122185 WASHINGTON</p> <p>* see p.2589, chart 1, p.2591, scheme 4,p.2596, table 5 *</p> <p>the whole document</p> <p>---</p>	8-19,62
X,P	<p>WO 98 56376 A (SUGEN INC) 17 December 1998 (1998-12-17) the whole document</p> <p>---</p>	39-50
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X	<p>WO 96 40116 A (SUGEN INC) 19 December 1996 (1996-12-19)</p>	39-50,62
Y	<p>* overlap of chemical formula, see claims 7,8,14,20, the definition of the substituent A *</p> <p>the whole document</p> <p>---</p>	51-61
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 99/06468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>MOHAMMADI M ET AL: "STRUCTURES OF THE TYROSINE KINASE DOMAIN OF FIBROBLAST GROWTH FACTOR RECEPTOR IN COMPLEX WITH INHIBITORS" SCIENCE, US, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE., vol. 276, no. 5314, page 955-960 XP002065235 ISSN: 0036-8075 * see p.956, SU5402 * the whole document</p> <p>-----</p>	39-62
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INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 63-104 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 20-38 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-19, 39-62
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 20-38

Present claims 8 -19 and 62 relate to an extremely large number of possible compounds with only a small part being fixed (see in particular the definition of p together with K and L). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of example 2, pages 92-94, see also examples of tables 10 and 11 (pages 27-29 e.g . those compounds prepared in these examples and closely related analogues/homologues compounds).

Present claims 1-7 and 62 relate to an extremely large number of possible compounds, with partially completely different chemical character, see claim 6). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of example 1 (pages 90-92 e.g those compounds etc. prepared in these examples and closely related homologous compounds etc.).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7,62

Tricyclic 3-methylene-2-oxindole based compounds of formula I and II

2. Claims: 8-19,62

Pyrazole-amide based compounds

3. Claims: 20-38,62

3-Tricyclic substituted 3-methylene-2-oxindole based compounds and intermediates for their production

4. Claims: 39-50,62

3-Monocyclic substituted 3-methylene-2-oxindole based compounds

5. Claims: 51-61,62

6-Phenyl-3-methylene-2-oxindole based compounds

INTERNATIONAL SEARCH REPORT

Information on patent family members			International Application No PCT/US 99/06468	
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members			International Application No PCT/US 99/06468	
Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
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Patent document cited in search report	Publication date		Patent family member(s)	Publication date
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